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Renal Failure Associated with Animal Toxins

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Abstract

Venomous and poisonous animals are a major cause of global morbidity and mortality with cardiovascular and renal toxicity as common presentation. Renal functional impairment as a result of their toxicity is manifested in form of specific histopathological changes. Regardless of vast mentioning of renal toxicity in literature previously, only few studies are currently available with an integrated approach. This paper mentions about various such animals with nephrotoxic potential describing the toxic principles in their venom and inflicted changes in renal pathology.

Keywords: Animal; Poisoning; Nephrotoxicity; Renal failure; Acute tubular necrosis

Introduction

Fatalities in human are caused by various venomous and non-venomous animals.[1] Animal toxins and venom are well acknowledged for their hazards to mankind. Animal toxins consists of enzymes, peptides and proteins that can cause cellular injury with a broad range of systemic manifestations such as cardiovascular and renal system.[2–4]

Prevalence of human exposure to such poisonous and venomous animals and recent awareness of their nephrotoxic manifestations has led to the recognition of toxic induced nephropathy. The kidney is susceptible to injury by due to its high vascularity, either by hemodynamic changes induced by toxin effects on ion channels, or by peptides and enzymes causing ischemia or by direct injury.[4]

Hemodynamic alterations, vasoactive and inflammatory mediators and direct nephrotoxicity are closely integrated to cause renal failure.[5]

Nephrotoxicity results directly from action of a toxin on the kidney from secondary acute tubular necrosis due to hypotension or rhabdomyolysis. Knowledge about these medically important venomous and poisonous animals will help in prevention, diagnosis and clinical management of their nephrotoxicity.[6]

We conducted a comprehensive search of literature for nephrotoxic animals in PubMed, ProQuest, Science Direct, Springer, ClinicalKey, Scopemed and Google Scholar. Most of the included studies were focused on nephrotoxic effects on human.

This paper by an integrated approach presents an overview various venomous and poisonous animals that have been recognized in the literature causing nephrotoxicity.

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Literature

Various pathological changes can occur in the kidney after exposure to animal toxins, which has a broad spectrum, and all renal structures can be involved. Envenomation and poisoning by these toxins from various animals is well documented. The toxic components of the venom, bites, stings, contact and ingestion of various such animals along with their nephrotoxic effect in form of renal pathological changes have been described here.

Reptile

Snakes

The World Health Organization (WHO) estimates there are between 81,410 and 1,37,880 deaths out of about 5.4 million snakebites occur annually.[7] Acute renal failure (ARF) is a common presentation of venomous snakebite like Viperidae and Elapidae bites and nonvenomous bites like sea snakes.[8]

Family Elapidae

Krait

The greater black krait, *Bungarus niger* which is commonly seen in India, Nepal, Bhutan and Burma, and *Bungarus candidus* and *Bungarus multicinctus* in Thailand and Vietnam have reported to cause rhabdomyolysis and consequent ARF. Main toxins present in the venom are bungaro toxins, phospholipases A2.[9]

Pseudonaja

Pseudonaja textilis, Eastern or Australian brown snake envenoming causes consumptive coagulopathy due to a potent prothrombin activator. Thrombotic microangiopathy characterized by thrombocytopenia with fibrin thrombi and red cell sludging in glomerular capillaries, microangiopathic hemolytic anemia, some apoptotic cellular debris and possible segmental early necrosis, resulting in ARF was also reported.[10]

Mulga snakes

Pseudechis australis has wide distribution in Australia. Venom includes mulgotoxin and myotoxic phospholipase which produce rhabdomyolysis and myoglobin cast nephropathy. Tubulopathy with tubular epithelial cell degeneration mostly involving proximal convoluted tubular necrosis, focal glomerular changes, including dilatation of Bowman's space and decline in number of glomerular tufts were noted. The proximal convoluted tubules showed features of tubular necrosis.[11]

Red-bellied Black snake

Pseudechis porphyriacus commonly seen in Australia envenomation resulted renal failure which revealed rhabdomyolyis and marked tubular necrosis with intraluminal occlusion subsequent to pigmentary casts. The major toxic component (pseudexin) takes the form of a mixture of three Phospholipase A2 isoenzymes, a factor Xa-like prothrombin activator and myotoxin.[12]

Tiger snake

Notechis scutatus (mainland tiger snake) and *Notechis ater* (black tiger snake) commonly occur in Australia. Thrombotic microangiopathy, which occurred with venom induced consumption coagulopathy, was characterized by ARF. Notexin is a neurotoxic and myotoxic phospholipase A2 derived from venom.[13,14]

Coral Snakes

Coral snakes are the American members of the family Elapidae represented by the genera Micrurus, Leptomicrurus and Micruroides. Micrurus snakes can be found in North America. Venom exhibited phospholipase and myotoxic activity. Kidneys presented with extensive tubular necrosis with fragmentation of nucleus, the brush border destruction, basal membrane rupture and tubular epithelial cells exfoliation, granular cast and tubular thickening. The histological features of the lesions suggest an important role of deposition of myoglobin in indirect damage to glomerulus.[15]

Taipan snake

Oxyuranus scutellatus, coastal taipan venom, contains mixture of toxins including taipoxin, a phospholipase A2 presynaptic toxin and myotoxin; taicatoxin, a calcium channel blocker and a prothrombin activator. It commonly exists in Australia. Renal failure exhibits as hemolytic uraemic syndrome with rhabdomyolysis and myoglobinuria.[16]

Family Viperidae

Adder

Vipera berus, common European adder, is the most widely distributed species of viper in Europe. It is a common venomous snake existing in England, Wales, and Scotland, envenomation of which results in ARF.[17] The venom of *V. berus* contains a complex mixture of high molecular weight proteins, predominantly proteases, hyaluronidase, peptide hydrolases, and phospholipases with predominantly hemorrhagic and cytotoxic effects.[18] *Bitis arietans* (Puff adder) found in savannah and grasslands from Morocco and western Arabia in Africa reported glomerulonephritis.[19] *Vipera raddei* (Armenian adder) is widely distributed in Armenia. The venom contains potent toxins and phospholipases. Light microscopy revealed thin capsule and weak disruption of the histological structure of kidney. Congestion of capillaries of the glomerular apparatus and vesicles of the middle and cortical layers were noted. Several nuclei in the lymphocytes between capillaries' loops and glomerular apparatus were found. The cytoplasm of proximal channels epitheliocytes was homogeneous. The channels were sporadically filled with homogeneous mass.[20] *Venom of Acanthophis antarcticus* (common death adder) from New Guinea contains myotoxic phospholipase A_2. Toxicity showed features of renal failure.[21,22]

Desert horned vipers

Cerastes gasperettii and *Cerastes cerastes* are the most common snakes of the Middle East, including Iraq and North Africa. Toxins present in venom includes serine proteases and other thrombinlike enzymes, fibrinogenases (IVa, Cerastocytin, Cerastotin, RP3 4, Afaaˆcytin and Cerastase F-4), which causes hypofibrinogenemia; platelet aggregation/ agglutination activators (Cerastocytin, Cerastotin); platelet aggregation inhibitors (IVa, Cerastatin, Cerastin), activators of Factor X (calcium-dependent and independent serine proteases, Afaaˆcytin), haemorrhagic protease (Cerastase F-4), protein C activator and an alpha-beta fibrinogenase (Afaaˆcytin); a phosphodiesterase exonuclease and a weakly toxic phospholipase A2. Envenomation by direct nephrotoxicity and ischemia results in mesangial proliferative glomerulonephritis resulting in acute tubular necrosis (ATN). Cortical necrosis resulting from thrombosis and bleeding was also noticed.[23]

Pit viper

Bothrops snakes, lance-headed pit viper belonging to genus Bothrops especially *Bothrops asper*/*B. atrox* cause nephrotoxicity. They are commonly seen in Central and South America mostly in Columbia, Mexico, Venezuela, etc. *Porthidium nasutum*, *B. puntacus* and *B. schlegelii* are other species. ARF occurs as a result of hypovolemia, or by the presence of nephrotoxic components in venoms or by the occurrence of disseminated intravascular coagulation (DIC) causing ischemic damage. Renal pathology demonstrates acute glomerulonephritis, ATN or cortical necrosis.[24] *Bothrops jararaca* is the most common species of Brazil. Its venom include metalloproteinases, serine-proteinases, C-type lectins and bradykinin-potentiating peptides; and *B. insularis* contains transcriptome.[25,26] *B. moojeni*, commonly seen in Brazil has potent phospholipase A2 and proteolytic activities which reported ATN and glomerulonephritis with mesangiolysis, glomerular microaneurysms, and glomerular basement membrane abnormalities.[27] *Hypnale hypnale*, hump-nosed pit viper bites causing ARF have been reported in India and Srilanka.[28]

Russell's viper

Daboia russelii russelii is widely distributed in India, Pakistan, Sri Lanka, Myanmar, Cambodia, Thailand, Indonesia, Southern China and Taiwan. Toxins commonly reported in venoms are the acidic and basic phospholipases A2, serine proteinase and metalloproteinase, phosphodiesterase, snaclec protein and L-amino acid oxidase. Procoagulant toxins such as Factor X activating enzyme induce intravascular clotting in the renal microcirculation, compromising the delicate renal perfusion.[29] Pathogenesis of ARF is associated to intravascular hemolysis, DIC, and also direct nephrotoxicity. Histopathology findings also reported necrotic changes in the tubular area.[30]

Saw scale viper

E. carinatus (carpet viper) is the most common snake in India. It also occurs commonly in Nigeria, Israel and Thailand. Hypotension in *E. carinatus* envenomation occurs due to bleeding either into tissues or externally. It can also occur due to release of bradykinin. The hypotension and circulatory collapse lead to ischemic ARF. Its venom directly activates prothrombin to thrombin. Viper venom produces Factor V activation with

fibrinolysis leading to DIC. This can result in hemorrhage, hypovolemia and thrombin in the microvasculature and capillaries of glomerulus and a microangiopathic hemolytic anemia with subsequent ARF. DIC plays a main pathogenetic role in snakebite induced cortical necrosis. Tubulointerstitial lesions, principally ATN were observed. Acute cortical necrosis occurs and can be patchy or diffuse.[31]

Rattle snake

Crotalus durissus, South American rattlesnake is commonly found in Brazil. Its venom is a complex mixture of toxins, enzymes, and peptides. The main identified toxins are crotoxin, crotamine, giroxin, convulxin, and kininogenases, phospholipases and hydrolases. Crotoxin is accountable for the high toxicity and has myotoxic, neurotoxic and nephrotoxic activity. Crotalid-induced ARF is connected to renal vasoconstriction, rhabdomyolysis, and a direct nephrotoxic effect of the venom. Crotoxin administration resulted in an increase in glomerular filtration rate attributed to direct effect on the glomeruli and further a rise in urinary flow rate by venom natriuretic peptides.[32,33]

Family Colubridae

Boomslang snake

Dispholidus typus, African tree snake is found throughout southern Africa. ARF with hematuria and hemoglobinuria often occurs due to envenomation. The boomslang venom is a potent procoagulant causing a consumption coagulopathy with resultant profuse hemorrhage.[34] Venom contains metalloproteinases. Renal pathogenicity is attributed to DIC caused by fibrinogen consumption and subsequent in coagulable blood with hemorrhage into muscle and brain tissues. Renal failure in form of ATN may also occur from pigment nephropathy.[35]

Keelback snake

Rhabdophis subminiatus, red-necked keelback snake belonging is common in Singapore and Netherlands. It reported acute kidney injury. Factor X activator in the venom induce severe hemorrhagic diathesis.[36,37]

Family Hydrophiinae and Laticaudinae

Sea snake

Sea snakes are widely distributed in the tropical Pacific and Indian Ocean. A toxic phospholipase A2 (PLA2-H1), in the venom of *Hydrophis cyanocinctus* cause myonecrosis and mild nephritis.[38] Proliferative glomerulonephritis and acute tubular degeneration in mice by the venom of *Apiysurus laevis* was also reported.[39]

Fish

Fresh water fish

Danio rerio, fresh water fish belong to the minnow family, Cyprinidae. Zebrafish larvae can develop cystic kidney disease. Lesions in genes involved in cilia formation and function result in the formation of cysts in the glomerular-tubular region.[40] Icthyotoxic acute kidney injury was observed after fish gall-bladder or raw bile ingestion. Toxin cyprinol sulphate causes ischemic ATN or acute tubule-interstitial nephritis. Renal failure by gall-bladder consumption includes fresh water fishes like grass carp, Ctenopharyngodon idellus in India and Pennsylvania, and Labeo rohita, other freshwater fish common in India, the black shark (minnow) fish, Morulius chrysophekadion and bony-lipped barb fish, Ostechilus melanopi in Vietnam.[41–43]

Phylum cnidarians

Sea Anemone

Night sea anemone, *Phyllodiscus semoni* is found commonly in Western Pacific ocean in Japan. Stings by these demonstrated in the renal pathology, mild ischemic changes in glomeruli, glomerular endothelial damage, thrombus formation, mesangiolysis, and partial rupture of glomerular basement membrane. Dilation of tubules or tubular degeneration and detachment of epithelial cells in the outer media were prominent suggestive of ATN. The venom extracted from the nematocysts (PsTX-T) and 115-kd protein toxin (PsTX-115) was nephrotoxic.[44,45]

Jelly fish

Cyanea capillata are common in China. Its tentacles cause marked renal morphological changes. Renal pathology reported partially destroyed glomerular capillaries or withdrawal of the capillary tufts, deposition of fibrin microthrombi in glomerular capillaries, and hyaline casts along with vacuolations in Bowman's capsule. In addition, severe proximal tubular degenerative changes occur characterized by cytoplasmic vacuolation, nuclear pyknosis and loss of proximal brush border. Few completely necrotic renal epitheliums in some

tubules, along with hyaline casts and detached cellular debris deposition in the collecting ducts and distal tubules was noted. Further, in some areas, diffuse congestion of peritubular capillaries and erythrocytes extravasation were also seen. Pore-forming toxins in the venom act by disrupting normal transmembrane ion concentration gradients in vulnerable cells. The Portuguese man-of-war (*Physalia physalis*) also reported acute tubular necrosis.[46]

Box jelly fish, *Chironex fleckeri* (sea wasps) occur commonly in Australia and Thailand, stings of which cause acute renal failure. The toxins are composed of a complex mixture of proteins and polypeptides, including cardiotoxic, hemolytic and dermatonecrotic toxins.[47] Jelly fish, *Stomolophus meleagris* or *Nemopilema nomurai* often seen in the China Sea showed renal failure with features of swelling of renal glomerulus, stricture of renal vesicle and dilatation of renal tubules. The several toxins in venom includes hemolysin, C-type lectin, phospholipase A2, metalloprotease, protease inhibitor and potassium channel inhibitor.[48]

Arthropod

Fire ants

Common group of ants seen in the United States of America is fire ants of Solenopsis species like the red fire ant, *Solenopsis invicta* or *Solenopsis wagneri*. Large doses of formic acid in these ants acts as mitochondrial cytochrome oxidase complex inhibitor causing tissue asphyxia, and subsequently cell death; resulting in rhabdomyolysis. The venom also constitutes nonproteinaceous alkaloid which cause local swelling and induce hemolysis. The pathogenesis of ARF is due to constriction of renal vasculature, formation of intraluminal cast, and direct tubular toxicity by heme proteins like myoglobin.[49]

Wasps and bees

Hymenoptera insects include Apidae (bees) and Vespidae (wasps and hornets). Stings by insect of order Hymenoptera like wasps (*Vespa orientalis*, *V. gnifica*), bees (*Apis mellifera*) and hornet have been reported in Australia, Sweden and India. ARF is infrequent with wasp bites and present as acute interstitial nephritis directly associated to the venom or tubular injury induced indirectly by immense hemolysis and rhabdomyolysis. Renal histopathology reported ATN, interstitial and glomerulonephritis.[50–52] Renal biopsy also revealed thrombotic microangiopathy with mild diffuse ischemic shrinkage, and interstitial ischemic tubular nephropathy with positive immunohistochemical staining of tubular granular casts with hemoglobin and myoglobin. Acute interstitial nephritis with infiltration of mononuclear cells with polymorphonuclear cells and eosinophils was also reported.[53] In ARF due to wasp and bees, toxic principles in venom include active amines such as serotonin, histamine, phospholipase A2, kinins, mastoparan, hyaluronidase, toxic surface-active polypeptides (apamine and mellitin). Phospholipase A2 triggers the release of arachidonic acid from lipid in the cell membrane which initiates production of inflammatory eicosanoids. Spread of venom is facilitated by action of hyaluronidase which causes breakdown of hyaluronic acid and chondroitins in the connective tissues.[50,51] The venom of *Vespa orientalis*, oriental hornet has a proteolytic activity on 14C-globin,which is inhibited partially by ethylenediamine-tetracetic acid and trasylol. Thus, the plasma coagulation factors activity is affected by both metaloprotease and serine activities.[53,54]

Brown Spider bites

Loxoscelism results from bites by spiders belonging to family Sicariidae, commonly known as brown spiders, recluse or fiddle-back spiders. In South America, it is caused by *Loxosceles intermedia and Loxosceles laeta* in Brazil and Argentina; and *Loxosceles gaucho* in Brazil, and in North America and Mexico, it is caused by *Loxosceles deserta and Loxosceles reclusa*. And in South Africa, Europe and South Australia, *Loxosceles rufescens* rarely reported cases. The principal components are phospholipase D, which cause dermonecrosis. Injection of venom triggers a complex inflammatory response, including the release of lipid mediators and pro-inflammatory cytokines. Additionally, the venom can result in complement activation and platelet aggregation by direct hemolytic effect on erythrocytes, and also increases the size of the tissue lesion attributed to hyaluronidase activity, which is a hallmark feature of loxoscelism. Systemic loxoscelism is characterized by renal failure with intravascular hemolysis. Rhabdomyolysis results in raise in creatine kinase which contribute to the acute renal injury.[55–57] *Loxosceles intermedia* venom contains sphingomyelinase D, Metalloproteases, hyaluronidase, lipase and alkaline phosphatase. Renal biopsy specimens on light microscopic analysis showed proximal and distal tubular hyalinization, interstitial edema, blebs and vacuoles in tubule epithelial cells, glomerular collapse,

erythrocytes in Bowman's space, and eosinophilic material deposition in the tubular lumen. Electron microscopic findings revealed disorders of the basement membrane and endothelial and glomerular epithelial cell cytotoxicity. Tubular epithelial cell cytotoxicity with increase in smooth endoplasmic reticulum, mitochondrial changes, cytoplasmic membrane blebs, autophagosomes along with tubular deposition of amorphous material was noted.[58]

Centipede

Bite of the giant desert centipede *Scolopendra heros* causes tubular necrosis. It is found in Arizona, southern California, Texas, Georgia, Alabama, Louisiana, Kansas and Mexico. ARF occur due to muscle injury and myoglobinuria. Hyaluronidase, Hemolytic phospholipase A, cardiotoxic protein and serotonin have been described in Scolopendromorph venoms. Furthermore, the toxin is referred cytolysin due to its ability to lyse cells. Some centipede venoms are complex mixtures containing histamine, 5-hydroxytryptamine, polysaccharides, lipids, and various enzymes such as proteinases.[59,60]

Caterpillars

A hemorrhagic syndrome caused by cutaneous contact with caterpillars of the species *Lonomia obliqua* has been observed in Brazil and other parts of South America. The toxin in the bristles contains mediators that initiate Factor XIII activation and cause intense intravascular coagulation. Enzyme serine-protease called Lopap in the extract of bristles is capable of thrombin activation, and result in micro-coagules formation which efficiently consume coagulation factors. Its venom also contains phospholipase A2, in addition to procoagulant serine and cysteine proteases. Acute renal failure with acute tubular necrosis is reported.[61]

Scorpion

Hemiscorpius lepturus is the most important scorpion in Iran. The venom from *H. lepturus* is primarily cytotoxic and has nephrotoxic, hemolytic, and hepatotoxic effect to some extent. Its venom has gelatinase, caseinase and hyaluronidase. Toxicity demonstrated ARF with hemolytic uremic syndrome with variable degrees of congestion and hemorrhage in kidney tissues.[62,63] *Tityus serrulatus*, yellow scorpion, is the most studied species in Brazil and other parts of South America. The histopathology revealed renal tubular protein deposit and perfusion of kidney urinary spaces with venom. Its venom contain pore-forming peptides which promote renal alterations with rise in perfusion pressure from increased vascular resistance resulting in decreased renal flow.[64] Venom of the Buthidae scorpion, *Buthus occitanus tunetanus* induce ARF in patients following severe scorpion accidents presenting peritubular congestion.[65]

Beetle

Cantharis Q is a crude alcoholic extract of *Lytta vesicatoria*, commonly known as the Spanish fly or blister beetle which carries venomous substance cantharidin in its hemolymph. It is commonly used as aphrodisiac. Cantharidin from *Mylabris cichorii* or *Lytta vesicatoria* or *Mylabris pustulata* causes tubular necrosis and glomerulonephritis. The histopathology revealed glomerular shrinkage with widening of Bowman's space, vacuolation, macrophages infiltration in the peripheral areas of glomerulus, and degenerative changes in the proximal and distal convoluted tubules.[66]

Conclusion

The renal pathology effected by animal toxins and venom has a wide spectrum, with involvement of all renal structures. This review by providing information about various animal envenomation and poisoning that exhibits nephrotoxic effects enables the health care providers to manage the morbidity and mortality due to renal failure. We expect that this review will further encourage the researchers to identify the specific nephrotoxic principles resulting in envenomation or poisoning. Further we hope this paper will enable toxicologist, pathologist, and health care providers in emergency medicine department in management of such cases.

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